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Title: Effect of formoterol alone and in combination with aclidinium on electrocardiograms in dogs

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Body: Introduction: Co-administration of a long-acting β-agonist with an anticholinergic is common clinical practice for the management of COPD, but there are concerns that systemic exposure to both drugs could cause undesirable pharmacodynamic effects on the heart. Aims: To evaluate the cardiovascular safety of formoterol alone and in combination with aclidinium in conscious dogs. Methods: Formoterol (1, 3, 10 μg/kg iv), aclidinium (50, 167 μg/kg iv) and formoterol+aclidinium (1+17, 3+50, 10+167 mg/kg iv) were administered to fasting, male Beagle dogs (n=4; 13–16 kg) in a 3-min perfusion. Each dog received each dose with >6-day washout. Electrocardiograms were recorded at baseline (for 1 h) and 24 h post-administration (for 90 min) and assessed for ventricular tachycardia (VT) and premature ventricular complexes (PVC). Results: Formoterol alone showed a dose-dependent trend to induce VT. VT was observed in 0, 1 and 4 animals treated with formoterol 1, 3 and 10 μg/kg, respectively. Aclidinium alone (both doses) did not induce VT. The combination of formoterol+aclidinium resulted in VT in a similar number of animals as formoterol alone (2 and 3 animals with 3+50 and 10+167 μg/kg, respectively). Similar results were observed for PVC. At the highest doses of formoterol and aclidinium, the plasma concentrations corresponded to 32 and 4000 times those reported in human plasma after clinically relevant doses. Conclusions: Addition of aclidinium does not alter the incidence or rate of formoterol-induced VT or PVC in dogs. These results suggest that aclidinium has no synergistic interaction on cardiac function with β-agonists. This study was supported by Almirall S.A., Barcelona, Spain.